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CME Review

Treatment of patients who present after an episode of anaphylaxis

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At the conclusion of this activity, participants should be able to:

- Establish a differential diagnosis for patients presenting to their practice with symptoms suggestive of a previous anaphylactic episode
- Institute an effective treatment program to prevent recurrent episodes of anaphylaxis and manage such an episode if there is a recurrence.

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Introduction

Allergists-immunologists see anaphylaxis from 2 perspectives. Because they administer immunotherapy, they deal with the treatment of the acute episode. Arguably, however, the most common encounter is with a patient who presents as a result of an

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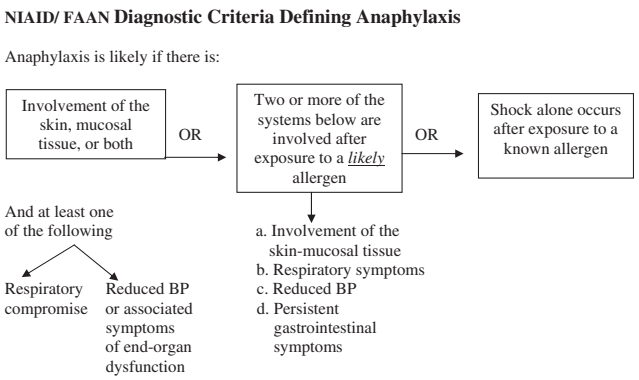

Figure 1. National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network diagnostic criteria defining anaphylaxis. BP indicates blood pressure. Modified and reproduced with permission from Table 1 in Sampson et al. Second Symposium on the Definition and Management of Anaphylaxis: summary report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. *J Allergy Clin Immunol*. 2006;117:391-397. NIAID, National Institute of Allergy and Infectious Disease; FANN, Food Allergy and Anaphylaxis Network; BP, blood pressure.

anaphylactic event. This article deals with the evaluation and management of such a patient.

Establishing the Diagnosis

To establish a diagnosis, one needs to be familiar with 2 things: the definition and the most common presenting manifestations of anaphylactic episodes. Defining anaphylaxis can be done in 2 ways: via its pathogenesis or its clinical presentations. Traditionally, it has been defined by its pathogenesis as "a systemic, immediate hypersensitivity reaction produced by immunoglobulin E (IgE-mediated) immunologic release of mediators from mast cells and basophils."[1] More recently, attempts have been made to define it by its various presentations, resulting in what is commonly referred to as the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria[2,3] (Fig 1). These criteria were established as a consensus derived from an NIAID/FAAN conference composed of participants of varying backgrounds and medical specialties. It was the intent of this conference to establish criteria that allergists, emergency medicine physicians, and other specialists could use to promptly recognize an episode of anaphylaxis. One of the outcomes was to establish a criterion that indicated the need for the administration of epinephrine.[4]

There has been some controversy over these criteria because at first glance they appear to rely on a 2-organ system manifestation to establish a diagnosis.[5] However, the authors recognized that these criteria may not capture all presentations that require the injection of epinephrine and that a single-system presentation can also serve as an indication for its administration: "There undoubtedly will be patients who present with symptoms not yet fulfilling the criteria of anaphylaxis yet in whom it would be appropriate to initiate therapy with epinephrine, such as a patient with a history of near-fatal anaphylaxis to peanut who ingested peanut and within minutes is experiencing urticaria and generalized flushing."[2] Also of note is that the NIAID/FAAN criteria have proven reasonably effective in confirming a diagnosis of anaphylaxis. In a study of episodes presenting to an emergency department (ED),[6] the criteria were found to have a sensitivity of 96.7% and a specificity of 82.4%. These results led to the conclusion that the "NIAID/FAAN criteria are highly sensitive but less specific and are likely to be useful in the ED for the diagnosis of anaphylaxis."[6]

Table 1
Signs and symptoms of anaphylaxis[a]

Signs and symptoms	Patients, %[b]
Cutaneous	
Urticaria and angioedema	61-90
Flushing	45-55
Pruritus without rash	2-5
Respiratory	
Dyspnea, wheeze	45-50
Upper airway angioedema	50-60
Rhinitis	15-20
Hypotension, dizziness, syncope, diaphoresis	30-35
Abdominal	
Nausea, vomiting, diarrhea, abdominal pain	25-30
Miscellaneous	
Headache	5-8
Substernal pain	4-5
Seizure	1-2

[a]This table was derived from the following: Lieberman P, Nicklas R, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol*. 2010;126:477-480; Wood R, Camargo CA, Lieberman P, et al. Anaphylaxis in America: results from a national physician survey. *Ann Allergy Asthma Immunol*. 2012;109(suppl):A20; and Boyle J, Camargo CA, Lieberman P, Sampson H, et al. Anaphylaxis in America: results from a national telephone survey. *J Allergy Clin Immunol*. 2012;129(suppl):AB132.
[b]Percentages are approximations.

Also, as mentioned, to establish a diagnosis, it is necessary to be familiar with the signs and symptoms of an anaphylactic event. These are listed in Table 1. It has long been believed that cutaneous and subcutaneous manifestations (flush, urticaria, pruritus, and angioedema) are the most common. However, their frequency of occurrence may be less than previously thought.[7,8] It is clear, however, that it is not necessary to have cutaneous symptoms to establish a diagnosis of anaphylaxis. In a recent survey, Anaphylaxis in America,[7] less than 80% of participants reported cutaneous manifestations, and in a recent review of ED visits only 62% of patients had hives or a rash.[8] So, clearly, anaphylaxis can occur in the absence of cutaneous manifestations. Nonetheless, when a large number of studies are reviewed, cutaneous and subcutaneous manifestations remain the most frequent.[1]

Taking a History

The history is perhaps the most important tool we have to establish the diagnosis and ascertain the cause of an event. The essential features of the history are listed in Table 2. The history should include a detailed evaluation of all potential causes with an emphasis on ingestants, including foods and medications, taken within 6 hours before the onset of symptoms. The activity the patient was engaged in at the time of the event should also be

Table 2
Essential features of the history in the evaluation of a patient who has experienced an episode of anaphylaxis

A.	Detailed history of ingestants (foods/drugs) taken within 6 hours before the event
B.	Activity in which the patient was engaged at the time of the event
C.	Location of the event (home, school, work, indoors, or outdoors)
D.	Exposure to heat or cold
E.	Any related sting or bite
F.	Time of day or night
G.	Duration of the event
H.	Recurrence of symptoms after initial resolution
I.	The exact nature of the symptoms (eg, if cutaneous, determine whether flush, pruritus, urticaria, angioedema)
J.	Assessing for physical factors or triggers
K.	In a female, the relationship between the event and menstrual cycle
L.	Was medical care given and what treatments were administered if so

noted, with special reference to exercise or sexual activity. The location of the event (home, school, work, indoors, or outdoors) should be established, and whether the patient was exposed to heat or cold at the time of the episode or experienced any preceding sting or bite should be noted. The time of day, duration of the event, and whether there was a recurrence of symptoms after initial resolution should be recorded. In a woman the history should include questioning as to the timing of the event(s) and the menstrual cycle. The exact nature of the symptoms should be pursued. For example, if cutaneous symptoms were present, whether there was flush, pruritus, urticaria, and/or angioedema should be determined. Any treatment given and whether the episode required medical attention is important.

Differential Diagnosis

The differential diagnosis is given in Table 3. In a significant number of cases the diagnosis will be evident and the cause will be apparent. This is often the case when the culprit is a food, drug, or flying Hymenoptera sting or fire ant bite. This is especially true in children because most events in children are due to foods.[8] However, in adults a large proportion of cases will be without known cause at the time the history is taken and in many instances will evade detection. Idiopathic anaphylaxis is fairly common in adults and can account for 60% of cases.[9]

A history of exercise-induced events may suggest a diagnosis of exercise-induced anaphylaxis or cholinergic urticaria. The latter is produced by any stimulus that causes sweating, occurring not only with exercise but also with anxiety and elevation of body temperature due to exogenous heat exposure. It has been traditionally thought that it is the elevation of core body temperature that produces sweating and urticaria. However, Casale et al[10] demonstrated that elevation of core body temperature produced by endotoxin that does not produce sweating failed to provoke urticaria. In addition, it is not completely clear that all patients with cholinergic urticaria who develop hives in stressful situations have a significant elevation in core body temperature. Therefore, there is some evidence, although perhaps controversial, that hives of cholinergic urticaria are caused by the act of sweating rather than sweating produced solely by elevation of core body temperature.

Exercise anaphylaxis exists in 2 forms: food independent and food dependent. In food-dependent cases, the patient is usually atopic, and the event occurs only with ingestion of a food to which the patient is sensitive followed by exercise. Neither exercise nor the ingestion of the food alone is sufficient to produce an event. Other physical factors, such as cold and sunlight, can cause events; thus, it is important to establish whether such exposures were present.

Flushing syndromes can often be confused with anaphylactic episodes. This is why a detailed history, as noted above, related to cutaneous manifestations is important. Prominent flushing points to a diagnosis of systemic mastocytosis or a mast cell activation disorder (MCAD), carcinoid syndrome, vasointestinal-polypeptide producing tumors, drug-induced flush, or alcohol related flush. Any of these entities can be confused with an anaphylactic event. Common causes of drug-induced flushing include niacin, nicotine, angiotensin-converting enzyme inhibitors, corticosteroids, and catecholamines.

In alcohol-related flush, a nonelevated, intense erythema appears over the face and trunk within minutes after the ingestion. Symptoms usually peak in approximately 30 minutes. There are 2 distinct forms. In one form, the flush is produced by the simultaneous ingestion of alcohol and certain drugs (eg, disulfiram, griseofulvin, and cephalosporins). In another form, the flush is due to a deficiency in acetaldehyde dehydrogenase 2, which catabolizes acetaldehyde. In its absence, blood levels of acetaldehyde accumulate, causing mast cell degranulation. It is most common in Asian people. Either type of flush can produce nausea, lightheadedness, and headache.

Table 3
Entities and causative agents to be considered when a patient presents with symptoms suggestive of an anaphylactic episode

Anaphylaxis
A. Anaphylaxis due to foods, drugs, insect stings
B. Anaphylaxis due to physical factors: exercise, cold, heat, sunlight
C. Idiopathic (cause undetermined) anaphylaxis
D. Vasodepressor reactions (vasovagal reactions)
Flushing syndromes
A. Carcinoid
B. Vasointestinal polypeptide tumors
C. Mastocytosis and mast cell activating syndrome
D. Medullary carcinoma of the thyroid
Restaurant syndromes
A. Monosodium glutamate
B. Scombroidosis
Nonorganic disease
A. Panic attacks
B. Munchausen stridor
C. Vocal cord dysfunction syndrome
D. Undifferentiated somatoform anaphylaxis
Miscellaneous
A. Hereditary angioedema accompanied by a rash
B. Paradoxical pheochromocytoma
C. Redman syndrome (vancomycin)
D. Capillary leak syndrome

Included under the rubric of restaurant syndromes are the reactions due to the ingestion of monosodium glutamate (MSG), sulfites, and scombroidosis. All of these are postprandial syndromes that can mimic anaphylactic events.

In susceptible individuals, the ingestion of MSG causes chest pain, facial burning, flushing, paresthesias, sweating, dizziness, headaches, palpitations, nausea, and vomiting. Sulfite reactions are uncommon since the removal of sulfite from salad bars. The ingestion of sulfites, however, can be associated with flushing and asthmalike symptoms.

In scombroidosis the symptoms are due to histamine or cis-urocanic acid found in spoiled fish. These agents are produced by bacteria such as *Morganella morganii, Klebsiella pneumoniae,* and *Hafnia alvei* in "spoiled" fish. It is most commonly caused by scombroid fish belonging to the family Scombridae (eg, tuna and mackerel) or Scomberesocidae (eg, saury), but nonscombroid fish, such as mahi-mahi, herring, and anchovies, can also produce episodes.

The features of scombroidosis are similar to those of anaphylaxis and can include cardiovascular, gastrointestinal, cutaneous, and neurologic manifestations. Episodes occur in outbreaks, and the morbidity on exposure can be as high as 100%. Symptoms can occur within a few minutes or several hours after the ingestion of the fish. The symptoms usually last only for a few hours but can persist for several days. The signs and symptoms are that of histamine toxicity and include urticaria, flush, angioedema, nausea, vomiting, diarrhea, and hypotension.

There are several features that distinguish scombroidosis from anaphylaxis. First, many people dining at the same table can be affected (anyone ingesting significant amounts of the fish). Second, the cutaneous symptoms are usually somewhat different, consisting of a prolonged flush with only modest or no urticaria. Finally, plasma and 24-hour urinary histamine metabolite levels will be elevated, but the serum tryptase level remains normal.

Not infrequently, nonorganic disease can mimic anaphylactic episodes. Such events can be involuntary as occurs in panic attacks, undifferentiated somatoform anaphylaxis,[11] and vocal cord dysfunction syndrome. On rare occasion, events can be self-induced as a variation of Munchausen syndrome.

Undifferentiated somatoform anaphylaxis is a term that describes manifestations that mimic anaphylaxis but lack objective

confirmatory findings. Like other somatoform disorders, this condition is related to psychological problems.

There are other conditions that can mimic anaphylaxis. For example, patients with hereditary angioedema can have an evanescent, serpiginous, erythematous rash that can be confused with urticaria. Other rare disorders, such as capillary leak syndrome and paradoxical pheochromocytoma, can also be confused with anaphylaxis.

Tests and Procedures to Establish the Diagnosis of Anaphylaxis and its Cause

Laboratory tests useful in establishing the diagnosis and cause of an anaphylaxis are listed in Table 4. The most useful laboratory test to confirm a diagnosis of anaphylaxis at the time of an event is usually serum tryptase measurement. However, at least in one study,[12] determination of plasma histamine was more sensitive than was serum tryptase. In this study, elevations of plasma histamine levels were observed in 42 of 97 patients, whereas only 20 patients had elevations of tryptase levels. Patients with elevated histamine level were more likely to have urticaria, more extensive erythema, abnormal abdominal findings, and wheezing.

Prostaglandin determinations are now available commercially and can be of value in diagnosing anaphylactic events.[13] In a study of patients with systemic mastocytosis who experienced anaphylaxis, it was found that mast cell activation may be manifested by a selective excessive release of prostaglandin D_2. Of note is that these patients responded to the administration of aspirin but not to antihistamines.[13]

Studies have reported that 24-hour urinary histamine metabolites are more reliable than the measurement of plasma histamine.[14] The advantage of measuring 24-hour urinary histamine metabolites rather than plasma histamine is the fact that by the time most patients are seen plasma histamine levels have returned to normal because they remain elevated for only 30 to 60 minutes. This is the reason that tryptase is measured in most instances rather than plasma histamine. Tryptase levels peak 60 to 90 minutes after the onset of symptoms and remain elevated for 5 hours or more.

Table 4
Tests useful in establishing a diagnosis of anaphylaxis, a condition mimicking anaphylaxis, or establishing the causal event

1. Establishing anaphylaxis as a cause
   a. During an event obtain:
      i. Serum tryptase
      ii. Plasma histamine
      iii. 24-hour urinary histamine metabolites
      iv. Prostaglandin D_2
2. Using the laboratory to establish a diagnosis of a condition mimicking anaphylaxis
   a. Serum serotonin
   b. Urinary 5-hydroxyindoleacetic acid
   c. Chromogranin A
   d. Vasointestinal polypeptide
      i. Substance P, vasointestinal polypeptide hormone, urokinase A, pancreastatin
      ii. Computed tomography, magnetic resonance imaging, single-photon emission computed tomography (octreotide or pentetreotide assisted)
   e. 24-Hour urinary catecholamines
   f. Serum catechols
   g. Plasma free metanephrine
3. Tests to establish the cause of anaphylactic events
   a. Skin tests to foods to drugs when indicated
      i. Skin tests using standard commercially available extracts
      ii. Skin tests using fresh food
   b. Serum specific IgE to foods and drugs when indicated
   c. Oral challenge
   d. Galactose 1,3-α-galactose
   e. Baseline serum tryptase
   f. Baseline 24-hour urinary histamine metabolites
   g. Prostaglandin D_2
   h. Bone marrow

Patients who have experienced an event should be given a letter stating that measurement of serum tryptase, plasma histamine, 24-hour urinary histamine metabolites, and perhaps prostaglandin D_2 (depending on the capabilities of the emergency department to obtain such tests) should be obtained at the time of any future event if there is any question that the previous episode was anaphylactic.

Further studies can be ordered should other diagnoses be suspected. For example, flushing without pruritus or urticaria suggests carcinoid syndrome or the presence of a vasointestinal polypeptide tumor or even perhaps a paradoxical reaction to a pheochromocytoma. In this instance, the measurement of neuropeptides can be helpful. Chromogranin A is a precursor to several functional peptides, including pancreastatin and vasostatin. It is elevated in carcinoid syndrome and also can be elevated in pheochromocytoma.

Other neuropeptides can be elevated in gastrointestinal-secreting vasointestinal polypeptide tumors. Such tumors produce abdominal cramping pain, diarrhea, nausea, and intermittent episodes of flushing. Measurement of neuroendocrine hormones, including vasointestinal polypeptide, neurokinin A, substance P, pancreastatin, and others, is readily available. In addition, computed tomography, magnetic resonance imaging, and single-photon emission computed tomography can be helpful. These tools can be assisted by the administration of octreotide or pentetreotide, which binds to tumors, enhancing their detection.[15] To diagnose a pheochromocytoma, 24-hour urinary catechols, serum catechols, and plasma-free metanephrine (the test of choice) are measured.[16]

Tests to establish the cause of an event include skin and in vitro tests for serum specific IgE to foods and drugs, serum IgE to galactose-α-1,3-galactose (α-gal), baseline serum tryptase, 24-hour urinary histamine metabolites, prostaglandin D_2, oral challenges, and, in some cases, a bone marrow determination. On occasion, fresh food prick-to-prick testing is more sensitive than testing with commercial extracts and has been used to identify a food culprit undetected via testing with commercial extracts.

Recent advances that have altered our approach to the use of the laboratory to establish a causative agent are the discovery of the role of α-gal and the recognition of the importance of mastocytosis and MCADs as causes of anaphylactic events.

In an elegant series of experiments Drs Thomas Platts-Mills and Scott Commins identified a novel IgE antibody to a mammalian oligosaccharide, α-gal, that has been associated with 2 distinct forms of anaphylaxis, an immediate onset of an event to cetuximab and a delayed onset of anaphylaxis, usually occurring 3 to 6 hours after the ingestion of mammalian food products (eg, beef and pork). This oligosaccharide, α-gal, is a major blood group substance of nonprimate mammals and is well known as a target of IgG antibodies, which are present in the sera of all immune competent individuals. Sensitization appears to occur through tick bites. The predominant cause of these IgE antibodies in the United States is bites from the Lone Star tick, *Amblyomma americanum*, but cases have been reported from other countries due to other species. It is interesting that this IgE antibody to α-gal cross-reacts with cat and dog but does not appear to pose a risk for asthma. However, it may impair diagnostic testing in some situations. Of importance is that IgE anti–α-gal is usually not detectable with skin tests using commercially available extracts of mammalian meat, but there is a commercially available test to detect serum specific IgE anti–α-gal. A significant number of previously considered idiopathic anaphylactic events are due to this mechanism.[17]

α-gal is suspect as a culprit in any case without known cause, especially in events occurring a few hours after eating, particularly those beginning in the early morning hours.

The realization that mastocytosis and MCADs can be responsible for episodes previously thought of as idiopathic has altered our

Table 5
World health organization (WHO) criteria for systemic mastocytosis[a]

Major criterion
The presence of multifocal dense aggregates of >15 mast cells as detected with tryptase or other special stains in bone marrow or other extracutaneous organs
Minor criteria
1. Atypical morphology or spindle shapes in >25% of the mast cells in bone marrow sections, bone marrow aspirate, or other extracutaneous tissues
2. Mutational analysis of KIT showing a codon 816 mutation (eg, Asp816Val) in bone marrow, blood, or extracutaneous organs
3. Bone marrow or other extracutaneous mast cells expressing the surface markers CD2, CD25, or both
4. Baseline serum tryptase levels >20 ng/mL.
The definitive WHO diagnosis of systemic mastocytosis requires the presence of 1 major and 1 minor criteria OR 3 minor criteria.

[a]Data are from Swerdlow SH, Campo E, Harris NL, et al. Mastocytosis (mast cell disease). In: *World Health Organization Classification of Tumours*. Vol 2. Lyon, France: IARC Press; 2008:54-63.

approach to patients. The seminal article establishing a relationship between mastocytosis and MCADs was published in *Blood* in 2007.[18] In this article, Akin et al found patients with idiopathic anaphylaxis had a clonal disorder of mast cells. They described 12 patients with idiopathic anaphylaxis who did not have the World Health Organization–defined characteristic bone marrow biopsies of mastocytosis (Table 5). However, some of the patients demonstrated 1 or more minor criteria for mastocytosis. Some of them were positive for the 816D>V mast cell–activating mutation. Since that publication, a number of other studies confirming this observation have been published. These observations have prompted a proposed change in the nosology and classification of anaphylactic events.[19] The new proposed nosology was derived at an international conference convened to establish consensus-based, evidence supported diagnostic criteria for mast cell–activating syndromes.

This proposed nosology suggests that mast cell–activating conditions be classified into 3 distinct categories: (1) mastocytosis and MCADs, (2) IgE-mediated anaphylactic events, and (3) idiopathic anaphylactic episodes. MCADs resemble mastocytosis and can cause anaphylaxis but lack sufficient bone marrow findings to make a diagnosis of mastocytosis according to the criteria established by the World Health Organization[20] (Table 5). Such patients have some of the bone marrow findings seen in mastocytosis and also can have gain in function mutations in kit. The diagnostic criteria for a diagnosis of a MCAD[19] are listed in Table 6.

The importance of the establishment that mastocytosis and MCADs can be the cause of idiopathic anaphylaxis lies in the fact that MCADs can, on occasion, be controlled with tyrosine-kinase inhibitors[18] and that, in the future, a tyrosine kinase inhibitor that is capable of controlling systemic mastocytosis may be developed.

Baseline, asymptomatic elevations in serum tryptase, plasma histamine, 24-hour urinary histamine metabolites, or prostaglandin D_2 suggest these conditions. The traditional cutoff value of 20 ng/mL used to establish an elevated level of serum tryptase may be too high. Mastocytosis and MCAD can be present in patients with lower levels of serum tryptase. A study of patients who had Hymenoptera anaphylaxis found a level of 11.7 ng/mL or higher was a marker for underlying mastocytosis.[21]

Because the only definitive way to make a diagnosis of mastocytosis is to perform a bone marrow biopsy, one is faced with the decision of whether to perform a biopsy in patients in whom no cause for anaphylaxis has been determined. When to do so remains a cause of debate.

Table 6
Suggested criteria for the diagnosis of mast cell activating syndrome[a]

1. Symptoms typical of those produced by mast cell degranulation
2. A substantial transient increase in mast cell mediators (a serum tryptase increase of 20% plus 2 ng/mL within 4 hours of an anaphylactic event)
3. A response to agents attenuating production of activities of these mediators or diminishing their effects on the target organ

[a]Data are from Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res*. 2001;25:603-625.

Prevention of Further Episodes

Table 7 lists measures to prevent further episodes of anaphylaxis.

Management of a Future Event Should it Occur

All patients who have had an episode should wear identification jewelry (eg, MedicAlert bracelet). This is especially important for patients who have experienced syncope. Use of any drug that would complicate therapy or tend to make the recurrent reaction more severe should be discontinued if possible. Risk-benefit analysis and consultation with the physician originally prescribing the drug are involved in the process of deciding whether it is in the patient's best interest to discontinue use of the particular drug in question. The drugs to be considered in this regard are β-adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin blockers, monoaminoxidase inhibitors, and certain tricyclic norepinephrine reuptake inhibitors (eg, amitriptyline).

β-Adrenergic blocking agents antagonize the β-stimulatory effects of endogenously secreted and exogenously administered epinephrine. Even if the β-adrenergic blocker is a selective cardiovascular blocker, it would still be relatively contraindicated because a cardiovascular response (as well as a pulmonary response) to epinephrine is essential in the treatment of anaphylaxis (as opposed to the treatment of asthma).

Angiotensin-converting enzyme inhibitors and angiotensin blockers block the compensatory response to hypotension that is induced by the activity of angiotensin 2. Angiotensin-converting enzyme inhibitors also have a second and perhaps more important effect. They prevent the catabolism of kinins, which are synthesized during an anaphylactic event.

Monoaminoxidase inhibitors and certain tricyclic antidepressants complicate the use of epinephrine because they can prevent its catabolism. Monoaminoxidase inhibitors do so by preventing its degradation by monoaminoxidase and tricyclic norepinephrine reuptake inhibitors by preventing the reuptake of norepinephrine at nerve endings.

The most important measure is to ensure that the patient is equipped with an automatic epinephrine injector and trained in its use. This training must emphasize that epinephrine is the only first-line drug for management of anaphylaxis and that it should be given immediately on the appearance of symptoms. It is well known via the work of Simons et al[22] that patients do not use their autoinjectors for many reasons. In a study of 1,885 participants who survived an anaphylactic event, nonusers of epinephrine

Table 7
Prevention of further episodes[a]

1. If the patient has experienced an episode to a drug, he/she should be educated regarding possible cross-reacting agents.
2. If a food was the cause, the patient should be educated about cross-reactivity of foods (eg, peanuts and lupin flour).
3. Use of drugs that place patients at risk for a more severe episode or complicate therapy should be discontinued if possible. Potential agents include:
a. β-Adrenergic blocking agents
b. Angiotensin-converting enzyme inhibitors
c. Angiotensin blockers
d. Monoaminoxidase inhibitors
e. Certain tricyclic antidepressants (eg, amitriptyline)
4. If the patient must be reexposed to a drug to which an event occurred, specialized procedures, such as desensitization and pretreatment, can be performed.

[a]For further discussion in regard to this table, see Lieberman P, Kemp SF, Oppenheimer J, et al. Beta-blockers and anaphylaxis: are the risks overstated? J Allergy Clin Immunol. 2005;116:933-936.

outnumbered those who administered the drug. Five hundred (27%) were epinephrine users, and 1,385 (73%) were nonusers. The groups were similar in regard to multisystem organ involvement and many other aspects of anaphylaxis; however, epinephrine nonusers reported not injecting epinephrine for various reasons, including the use of an histamine$_1$-antihistamine (38%), no prescription for epinephrine (28%), and/or what was perceived to be a mild anaphylaxis episode (13%).

Antihistamines are not appropriate substitutes for epinephrine. The median times to cardiovascular and/or respiratory collapse during anaphylactic episodes are 10 minutes for iatrogenic events, 15 minutes for field insect stings, and 30 minutes for food.[23] The onset of pharmacodynamic activity of antihistamines is far too slow to be an effective therapy to prevent mortality.[24] In addition, they antagonize only the effect of histamine, and clearly other mediators are involved and correlate with fatalities and the severity of events.[25] The onset of pharmacodynamic activity of epinephrine is within 10 minutes, and epinephrine is not a specific receptor antagonist but acts as a direct agonist with multiple activities, all of which antagonize the pathophysiologic events that occur during an anaphylactic episode.[26]

There are cogent reasons for a patient to always have 2 automatic epinephrine injectors available at all times. Two injections are necessary in up to 30% of episodes.[27] They may be necessary because of the severity of an event or because of a recurrence of symptoms after remission or a protracted event. In addition, in rare instances there may be failure of an injector to activate, and finally, an error may be made during the attempt to give the first injection.[28]

Patients should be told to either proceed to the nearest medical facility or call emergency services after injecting. They should assume the recumbent position with feet elevated if respiratory symptoms permit. They should remain recumbent until full cardiovascular stabilization has occurred. Fatalities have been associated with the resumption of erect posture before recovery.[29] A second injection can be given in 5 to 10 minutes after the first injection if no improvement has occurred. The patient should be told that the reason they need to go to a medical facility or call for emergency services is that further therapy may be needed. Patients have misinterpreted the reason for being told to seek help, thinking that the administration of epinephrine was dangerous, and therefore they had to be observed afterward. This has made them reluctant to use the drug. The reason to obtain help is because epinephrine therapy alone may be insufficient as therapy. Fatalities have been recorded even after the appropriate administration of this drug.[30]

Conclusion

Allergists-immunologists, probably more so than any other specialists, treat patients who have experienced an episode of anaphylaxis for the purpose of confirming the diagnosis, determining the etiologic agent, instituting a treatment plan to prevent further episodes, and adequately treating such an episode should it recur. The history is the most important tool to confirm the diagnosis and establish the culprit, but laboratory tests have become increasingly helpful tools to achieve these goals. Recent advances regarding the role of IgE anti–α-gal and our knowledge regarding mastocytosis and MCAD have amplified the role of the laboratory in this regard.

Epinephrine is the only first-line agent that should be used to treat a recurrent event, and all patients who have experienced an anaphylactic episode should be supplied an automatic epinephrine injector, keep 2 injectors available with them at all times, and be well instructed in the use of this agent.

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